REMARKS

Claims 1-8, 13-21 and 24-25 are pending in the application. Claims 9-12 and 22-23 have been canceled without prejudice. The amendments to the claims are made to merely further clarify the presently claimed invention. Support for the newly added claims 24 and 25 find support in claim 5 as originally presented. No new matter has been introduced, and entry of the above revised claims is respectfully requested.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 3-4, 6, 9, 15-16, and 18 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

The Examiner has criticized claims 3, 4 and 9 for reciting "gene carrier . . . is a vector or recombinant virus". It is believed that the amended claims 3, 4 and 9 overcome this rejection.

The Examiner has criticized claims 6, 15 and 16 for lacking antecedent basis for "cells" and "solid tumor" in claim 1. It is believed that the amended claims 6, 15 and 16 overcome this rejection.

The Examiner asserted that claim 18 is indefinite because "preventing or treating a solid tumor" is done to a subject or a patient having solid tumor. It is believed that the amended claim 18 overcomes this rejection.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-23 have been rejected under 35 U.S.C. §112, first paragraph because of lack of enablement for "prevention of any tumors, using any gene carrier, and any method of administration" (page 4, Office action April 13, 2009). Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

The Examiner indicated that the specification provides enablement for

> "a composition or agents of human apolipoprotein (a) kringle KIV9-KIV10-KV (LK68) or KV (LK8) and a method of treating solid tumors with AAV or Adenoviral viral vectors as gene carriers and administered to site of solid tumors by direct injection" (page 4, Office action April 13, 2009)

Support for "gene carrier"

Regarding the Examiner's allegation of lack of enablement for "gene carrier", the Examiner is reminded of the standards for determining enablement of the claimed invention.

> While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. (**MPEP § 2164.04**)

Applicants have provided a sufficient number of working examples of gene carriers to satisfy the enablement requirement. Undue experimentation for using various gene carriers would not be necessary to practice the claimed invention because making and using various gene carriers would be predictable given the present disclosure. Various examples show that the gene carrier vector harboring genes encoding LK8 or LK68 are predictably effective against tumor cells. Applicants have provided experiments of AAV, Adenovirus, Retrovirus and plasmid as a gene carrier.

Retrovirus is discussed in Examples 1 to 4 in which Applicants infected a cancer cell line with a retroviral vector comprising a gene encoding LK8 or LK68 protein, then selected cancer cells stably expressing the gene. The cells were injected into animals. The animals transplanted with the cancer cells stably expressing the gene encoding LK8 or LK68 protein showed inhibition of growth of the cancer cells. Plasmid vector use is discussed in Example 9-3. And further, the Examiner's attention is directed to the Jo Declaration filed December 7, 2008 in support of using plasmids as gene carrier. Accordingly, the present Specification fully enables the scope of the claimed invention.

Support for "parenteral administration"

The Examiner indicates that the Specification is enabling only for "direct injection" of the gene carrier. In response, Example 9-3 in the present Specification shows successful hydrodynamic injection of plasmid vector harboring gene encoding LK8 or LK68 into the tail

vein of mice. The Specification shows efficient expression of LK8 or LK68 protein in blood through intra-vein injection. Thus, Applicants submit that the method of administration should not be so limited to direct injection method as it would not require undue experimentation to administer the inventive gene construct parenterally to result in successful efficacious expression of the protein. Accordingly, the present Specification fully enables the scope of the claimed invention.

Rejection Under 35 U.S.C. §103(a) Over Chang (WO 01/19868 A1) In View of Trieu (1999, Biochem. Biophys. Res. Comm. 257:714-718) and Kikuchi (2002, Blood 100:3950-3959)

Claims 1-23 have been rejected under 35 U.S.C. §103(a) as being obvious over Chang in view of Trieu and Kikuchi. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Chang

Chang discloses LK8 and LK68 proteins. However, Chang fails to disclose a genetic construct for gene therapy for these proteins.

Trieu

Trieu discloses that a nearly full-size apo(a) protein (18 kringle IV repeats and 1 kringle V) expressed in a transgenic mouse delays tumor growth.

However, a much shorter version comprised of 6 kringle IV and 1 kringle V (termed Ha6) does not suppress tumor growth (Figure 1). At page 715, right column, Trieu states:

> This observation provides unprecedented evidence that a large number of kringle IV repeats is necessary for the biologic activity of apo(a) as an inhibitor of tumor angiogenesis and growth; . . . (emphasis added)

At page 715, right column, Trieu states:

> "thus, the observed lack of anti-tumor effects with this truncated apo(a) protein [Ha6] may be due to its inability to interact with tumor blood vessels.".

In the paragraph bridging pages 716 and 717, Trieu explains this "inability to interact with tumor blood vessels," as follows:

> . . . however, it is of interest that only full-length apo(a) localized to tumor micro-vessels. The fact that truncated apo(a) did not localize to tumor micro-vessels suggests that the missing kringle IV domains are necessary for the binding of apo(a) to tumor micro-vessels to exert its anti-angiogenic effects. (emphasis added)

Trieu fails to disclose or suggest making a gene construct that includes a gene encoding short-length kringle domain such as encoding LK8 or LK68 as in the presently claimed invention.

Kikuchi

Kikuchi discloses a vector comprising the NK4 full length gene, which includes NH_2 terminal hairpin domain and four (4) subsequent kringle domains of hepatocyte growth factor. Kikuchi discloses making AdNK4, which is a replication deficient adenovirus carrying NK4 cDNA. The vector was injected into various cancer model mice. Kikuchi discloses that administering protein form of NK4 inhibits tumor vascularization and induces apoptosis and necrosis of tumor cells. However, AdNK4 single therapy has virtually no therapeutic effect in the murine allograft tumor model. Kikuchi further discloses that tumor size is reduced when AdNK4 construct is injected in combination with T-lymphocyte stimulating dendritic cells (See Fig. 5 of Kikuchi).

Kikuchi fails to disclose or suggest making a gene construct that includes a gene encoding short-length kringle domains such as encoding LK8 or LK68 as in the presently claimed invention.

Distinctions of the Presently Claimed Invention Over the Cited References

The Examiner has failed to establish *prima facie* obviousness of the presently claimed invention. The Examiner is reminded of the standards for establishing obviousness.

> To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based

> upon applicant"s disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. (MPEP 2142)
>
> When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must reconsider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of all the evidence, including the evidence submitted by the examiner and the evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of obviousness was reached, not against the conclusion itself. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). (MPEP 2142)

The instant rejection is based upon the contention that it would have been obvious to one of skill in the art to place sequences encoding LK68 and LK8, as reported by Chang into the vector constructs of Trieu, Kikuchi, or Kuo (cited previously) with the expectation of using them as gene carriers to increase the efficacy of tumor gene therapy. The Examiner appears to believe that therapeutic use of vectors is routine in the art.

Chang discloses anti-angiogenic effects of LK8 and LK68. However, Chang fails to disclose a genetic construct for gene therapy for these proteins. Trieu is cited to remedy this deficiency by pointing to successful anti-angiogenic effects of full length apo(a) in transgenic mice. However, Trieu discloses that a gene vector including an apo(a) fragment of 6 kringle IV and 1 kringle V does not suppress tumor growth. Trieu cites the necessity for a gene fragment of apo(a) that is longer than this failed fragment. Trieu affirmatively guides the person of ordinary skill in the art to create anti-angiogenic fragments of apo(a) that are longer than 6 kringle IV and 1 kringle V. Trieu bluntly states that "the missing kringle IV domains are necessary for the binding of apo(a) to tumor micro-vessels to exert its anti-angiogenic effects." (see paragraph bridging pages 716 and 717).

In order to further remedy the deficiencies in Chang and Trieu, the Examiner cites Kikuchi and states as follows at page 9 in the Office action of April 13, 2009:

> However at the time of invention Kikuchi teaches tumor therapy with using kringle-4 containing fragments. Kikuchi teaches gene therapy of tumor using Adenovirus vector containing gene encoding NK4 kringles, short Kringle-4 containing fragments (entire article; abstract)

The Examiner further applies Kikuchi to the claims by stating the following in the paragraph bridging pages 9 and 10 in the Office action of April 13, 2009:

> Thus it would have been obvious to one of skill in the art to try gene therapeutic approach that would parallel the success of polypeptide therapy using LK8 and LK68 apo(a) protein kringle fragments as taught by Chang and further substitute the same for full length apo(a) gene therapeutic vector construct of Trieu or short kringle coding sequences in viral vectors described by Kiuchi or other gene therapy vectors taught by Kuo and prepare and use a composition to treat a solid tumor in an animal subject. One

The Examiner states that Kikuchi discloses gene therapy using Adenovirus vector containing "short Kringle-4 containing fragment" and that the claimed invention directed to gene carrier comprising gene encoding LK8 or LK68 (which are very short fragments of apo(a)) is obvious because Kikuchi discloses a gene therapy vector comprising a "short Kringle-4 containing fragment".

The references fail to be combinable with each other

The references fail to be combinable with each other for the following reasons. First of all, Kikuchi discloses using NK4 protein, which is not an apo(a) protein of Chang and Trieu references. Therefore, this raises an immediate issue of combinability of the Kikuchi reference with the Chang and Trieu references. A person of skill in the art making an apo(a) fragment would not look to a reference disclosing the manipulation of NK4 protein for any guidance. Therefore, these references fail to be combinable with one another.

Secondly, the Chang reference discloses a short LK8 (1 kringle) and LK68 (3 kringles) kringle domain peptide fragments. Trieu discloses the "necessity" of using genes encoding large fragments of apo(a) having more than 6 kringle IV's. By the very nature of these disclosures, Chang and Trieu fail to be compatible or complementary with each other as they disclose opposite results. And Kikuchi discloses an entirely different protein. Accordingly, the presently claimed invention is not obvious over the cited references.

Even if combined, the references fail to arrive at the presently claimed invention

The deficiencies of Chang and Trieu references are discussed above. However, Applicants fail to understand the Examiner's characterization of the Kikuchi reference and its relevance to the presently claimed invention. As far as Applicants can see, Kikuchi discloses making a vector that includes full-length NK4. Kikuchi fails to disclose or suggest breaking up the full-length NK4 protein in any way. Kikuchi fails to disclose or suggest inserting any single or short kringle-4 domain into a gene vector.

NK4 protein is a variant of Hepatocyte Growth Factor (HGF) protein. Contrary to HGF, NK4 full length version has anti-angiogenic activity. The NK4 gene cloned into the gene vector recited in Kikuchi is not a single kringle domain but rather a protein similar to the full length HGF comprising N-terminal hairpin loop and 4 kringle domains. Its molecular weight is 67 kD while that of full-length HGF alpha chain is 69 kD.

Kikuchi discloses that intratumoral injection of Ade-NK4 (Adenovirus/full-length NK4 construct) has little effect on the size of the tumor. Kikuchi discloses that tumor size is reduced when Ade-NK4 construct is injected in combination with T-lymphocyte stimulating dendritic cells. Therefore, the point of the Kikuchi reference is that dendritic cells contribute to anti-angiogenic effect of an otherwise weakly effective Ade-NK4 gene construct.

Moreover, Merkulova-Rainon et al., J. Biol. Chem, 278(39): 37400–37408, 2003 (Exhibit A) discloses that N-terminal hairpin loop rather than any 4 kringle domains is important for anticancer activity of HGF (Abstract).

Given that Chang fails to disclose or suggest a gene therapy vector housing a gene encoding LK8 or LK68, and Trieu guides the skilled artisan to make a vector incorporating only genes encoding large fragments of apo(a), and further Kikuchi discloses an unrelated NK4 gene having 4 kringle domains, and which further fails to disclose or suggest constructing a gene therapy vector including a small fragment of apo(a) gene such as LK8 (1 kringle V) or LK68 (2 kringle IVs and 1 kringle V), the combination of the references fails to arrive at the claimed invention. Therefore, the presently claimed invention is not obvious over the cited references.

Additional considerations

Teaching away of the Kuo reference

In the various communications with the Patent Office, Applicants particular disagree with one line of reasoning given by the Examiner. When a reference that "teaches away" from the claimed invention is cited to the Examiner, the Examiner argues that the reference is not a "teaching away" but rather the reference would further motivate the person of skill in the art to overcome the deficiency in the reference to make the claimed invention.

Examples of this situation is found with the Examiner's citation of Kuo (see above) and the Examiner's characterization of Trieu. Discussing Kuo first, Applicants had initially brought the Kuo reference to the attention of the Examiner in the Amendment filed on December 7, 2007, to show that Kuo reports that an adenovirus based vector system used to express endostatin or angiostatin demonstrates little or no inhibition of tumors in an animal model despite potent antitumor effects of endostatin and angiostatin when the protein is delivered directly.

The Examiner dismissed the Kuo reference that shows a failed gene therapy attempt and instead cited this reference against the presently claimed invention as exemplifying various gene therapy vectors that could be used in making the gene construct of the presently claimed invention. In the interview held on June 26, 2008, when confronted with the disclosure in Kuo that employing these vectors in expressing endostatin and angiostatin fails to result in any effective antitumor effect, the Examiner indicated that Kuo actually provides motivation to a person of skill in the art to insert the gene encoding LK8 and LK68 in a gene therapy vector instead of endostatin and angiostatin because LK8 and LK68 were shown by Chang to have anti-angiogenic activity at the peptide level.

However, the Examiner is reminded that endostatin and angiostatin also has anti-angiogenic activity when the protein is administered. The surprising finding in Kuo is that the gene therapy vector containing the gene encoding endostatin and angiostatin unexpectedly does not exhibit anti-tumor effects even though the genes are expressed and are present in the serum. So, why would a skilled artisan expect a vector construct harboring gene encoding LK8 or LK68 to have any different effect than portrayed in Kuo for the failed endostatin and angiostatin genes? Where is the reasonable expectation of efficacious success of a gene therapy construct by including a gene encoding LK8 or LK68? The Examiner's suggestion that the person of skill in the art would have been motivated to insert LK8 or LK68 gene into Kuo's failed gene therapy

vector with a reasonable expectation of success is on its face an improper application of the standards of establishing obviousness under 35 U.S.C. 103(a).

If LK8 or LK68 genes were indeed placed in the vectors described in Kuo, would a person of skill in the art reasonably expect to obtain effective tumor suppressing activity? The answer must a resounding "No", because Kuo already demonstrates that these vectors are not successful in suppressing tumor growth even though the endostatin and angiostatin proteins that are expressed from the gene therapy vector are observed in the serum of the infected mice (page 4609, left column). The Examiner is reminded that both endostatin and angiostatin possess kringle domains. The gene therapy vectors that are cited in Kuo may work for some genes, but certainly does not work for endostatin and angiostatin. The Examiner's decision to simply waive off the Kuo reference is contrary to law. The Examiner is required to consider the totality of the evidence presented in considering obviousness of the presently claimed invention.

The only expectation of success is found in the instant application, where there is demonstration of successful use of nucleic acids to express LK68 and LK8. With such success, no more than routine and repetitive experimentation is needed to practice the claimed methods.

Teaching away of the Trieu reference

When it was pointed out to the Examiner that the Trieu reference taught away from the claimed invention directed to gene therapeutic expression of LK8 (1 kringle) or LK68 (3 kringles), which are short fragments of apo(a), the Examiner simply waived off this argument without an explanation and again stated that Trieu is a disclosure that would motivate a person of skill in the art to actually insert LK8 or LK68 gene in a gene therapeutic vector. Applicants fail to see how a reference that expressly teaches that in order to make an anti-angiogenic fragment from apo(a), it is "necessary" to make it longer than a 7 kringle fragments, could somehow be used to obviate the claimed invention directed to a fragment of apo(a) that is much shorter than the Trieu fragment. Trieu says that it does not expect any fragment of apo(a) that has 7 or less kringle domains to have anti-angiogenic activity. The presently claimed invention has 1 kringle fragment (LK8) and 3 kringle fragments (LK68).

The Examiner argues that in spite of this negative teaching of Trieu, since Chang does disclose that small LK8 and LK68 protein fragments do have anti-angiogenic activity, a person

of skill in the art reviewing both Chang and Trieu would be motivated to include the gene encoding LK8 or LK68 into the vector of Trieu, even if Trieu in effect expressly discloses that a gene encoding LK8 or LK68 would not be expected to be effective to suppress tumor growth.

The Examiner has failed to consider the totality of the evidence. The Examiner chose to focus on the protein effects of Chang, but failed to consider the deeper ramifications of kringle expression through gene therapeutic vehicles. Kuo is a case in point as discussed above regarding the disparity between protein administration activity and gene therapy activity.

When Chang and Trieu are combined with the teachings of Kuo, a person of ordinary skill in the art would come to the conclusion that even though Chang discloses LK8 and LK68 peptides as having anti-angiogenic activity, a level of reasonable expectation of success would not be achieved within gene therapy context based on at least two considerations: (1) Kuo states that there is a disparity between protein administration activity levels, and gene therapy approach; and (2) Trieu states that anti-angiogenic fragment of apo(a) to be effective in a gene therapeutic setting must possess more than 6 kringle IV domains. A person skilled in the art, armed with the knowledge that gene therapeutic effects are not readily predictable from protein administration effects would have doubts of the likelihood of success that LK8 or LK68 would be effective in a gene therapy protocol of Trieu. Therefore, given the totality of the evidence, the presently claimed invention is not obvious over the cited references.

State of the art at the time of the invention regarding angiogenic or anti-angiogenic activity of apo(a) was confusing

As discussed above, the apo(a) art as well as proteins that possess kringle regions, exhibit unusual and sometimes inconsistent results. This results in an unsettledness and predictability of the activities of: (i) apo(a) protein, (ii) apo(a) fragments, and (iii) genes encoding apo(a) or apo(a) fragments. The activities of these molecules often do not correlate with each other. Some of the inconsistent activities are known in the art. A brief discussion follows:

Trieu discloses that the full length apo(a) is an anti-angiogenic protein. Other references disclose that full-length apo(a) has angiogenic activity.

Yano et al., "Stimulatory effects of lipoprotein(a) and low-density lipoprotein on human umbilical vein endothelial cell migration and proliferation are partially mediated by fibroblast growth factor-2", Biochim. Biophys. Acta 1998;1393:26–34 (Exhibit B) discloses the opposite effect from Trieu. Yano discloses that full length apo(a) is an angiogenic protein.

In Liu et al., "Apolipoprotein(a) stimulates vascular endothelial cell growth and migration and signals through integrin αVβ3", Biochem. J. 2009;418:325–336 (Exhibit C), the authors identified a stimulatory effect of apo(a) and Lp(a), but not LDL, on HUVEC proliferation and migration, which suggests a potential role for apo(a) in regulating important physiological/pathological events including angiogenesis, tumor invasion and metastasis, and wound healing. Liu discloses that apo(a) stimulates HUVEC proliferation and migration, and furthermore, induces angiogenesis, tumor invasion and metastasis, and wound healing. It also demonstrates that the LBS in the KIV10 and in the KV, which also constitute LK8 and/or LK68, are essential for these apo(a) activities. Lieu discloses that apo(a) is a stimulator rather than inhibitor, of angiogenesis.

Lou (Exp. Mol. Pathol. 65(2): 53-63, 1998) (Exhibit D, Abstract only) also reports that apo(a) is a stimulator of angiogenesis.

Given the above divergent results obtained regarding the activity of full length apo(a), a person of skill in the art would be confused as to the role of apo(a) in angiogenesis, and further would be dissuaded from making any gene therapeutic constructs including these genes encoding the various fragments. Indeed, the Chang reference may be confusing to the skilled artisan given the background and dislosures of apo(a) above, especially in view of Trieu, which discloses that a fragment as close to the full length must be used for anti-angiogenesis activity, which is a directly opposite teaching from Chang. Therefore, a person of skill in the art would be dissuaded from making a gene therapeutic construct given the overall uncertainty associated with the function of apo(a).

Gene therapy and protein therapy do not yield similar results

As discussed above, gene therapeutic effects are not readily predictable from protein administration effects. The following is a short discussion of the state of art.

The Kuo reference discussed above discloses that whereas angiostatin, endostatin, and neuropilin has good effects when protein is administered, they are significantly less effective when the subject is transfected with adenovirus harboring the genes encoding these proteins. Kuo states the following in the abstract, "these data underscore the need for comparative analyses of different therapeutic approaches that target tumor angiogenesis.

Joseph (Cancer Gene Therapy, 10: 859–866, 2003) (Exhibit E) also discloses that in the case of angiostatin, whereas the protein version of Kringle 1-3 had anti-angiogenic effects, the gene therapeutic construct of Kringle 1-3 resulted in no delay in tumor growth.

Given this divergent angiogenic/anti-angiogenic results obtained with administering the protein as opposed to the gene construct encoding these proteins that comprise kringle domains, it must be questioned whether a successful gene therapeutic effect is predictable from the protein administration effects in this field. Applicants submit that there is enough variability in the field to indicate that it would be unpredictable to automatically assume that a gene therapeutic construct would successfully follow in the activity path as administering the protein alone.

Unexpectedly superior activity of LK8 and LK68 expressed from gene construct over the Chang peptides

Applicants submit herewith a 132 Declaration of Dr. Eui-Cheol Jo, an inventor in the present application showing unexpectedly superior cell migration inhibiting activity of the LK8 and LK68 protein expressed from mammalian gene constructs harboring nucleic acid encoding LK8 or LK68 in mammalian cells. Adenovirus and AAV expressed LK8 and LK68 peptide prevented migration of endothelial cells at an unexpectedly high level compared with LK8 and LK68 peptides produced from *E. coli* as in Chang.

While it is well known that proteins produced from mammalian cells tend to have higher activity than those produced from *E. coli*, usually due to glycosylation and so forth found in proteins produced from mammalian cells, Dr. Jo provides evidence in the Declaration that indeed a 100 fold increase in activity was obtained and that this increase was not due solely to conventionally understood glycosylation of the proteins.

The unexplained and remarkably superior activities of LK8 and LK68 expressed from a gene construct in mammalian cells may explain why the therapeutically active levels of the inventive gene expressed LK8 and LK68 is much higher than at protein administration levels. Clearly, LK68 and LK8 peptides produced in mammals are fundamentally different in size and activity from *E. coli* produced LK8 and LK68 peptides such as disclosed in Chang, but such high activity could not have been predicted even with the general knowledge in the art that mammalian cell processed proteins have a different activity from *E. coli* produced cells. Quite simply, a 100 fold increase in activity of the gene construct of LK8 and LK68 over protein administration constitutes an unexpectedly superior result. But this result is made even more surprising considering the fact that Kuo had indicated that gene therapy results would not likely be successful even if the protein administration may be effective, and that Trieu discloses that an apo(a) fragment of less than 6 kringle domains would not have anti-angiogenic activity. Accordingly, the presently claimed invention is not obvious over the cited references.

Double Patenting Rejection

Claims 1-4 and 8-10 have been rejected under the obviousness-type double patenting as being unpatentable over claims 3-4, and 11-12 of Patent No. 6,743,428. Applicants point to the prosecution history in the Chang (6,743,428) patent, in which a restriction requirement had issued in this application on November 2, 2002, in which the Examiner had indicated that a cDNA construct was a different invention from the polypeptide claimed subject matter. Therefore, it would now be inconsistent with the prosecution history of the Chang (6,743,428) patent application to reject the presently pending claims under the obviousness-type double patenting.

Conclusion

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is hereby authorized to charge JHK Law's Deposit Account No. **502486** for such fees required under 37 CFR §§ 1.16 and 1.17 and to credit any overpayment to said Deposit Account No. **502486**.

Respectfully submitted,

JHK Law

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